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Disease-a-Month

Pulmonary Embolism and Infarction

JOHN B. HICKAM
HERBERT O. SIEKER

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Pulmonary Embolism and Infarction

JOHN B. HICKAM
HERBERT O. SIEKER

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PULMONARY INFARCTION AND CONGESTIVE HEART FAILURE 31

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PULMONARY EMBOLISM is a common and dangerous disorder. It has been found to account for roughly 4% of the deaths in a general medical and surgical hospital (40), and in custodial institutions the mortality from this cause is even higher (50). Although certain groups are known to be particularly liable to the development of venous thrombo-embolism, general prophylactic measures have not been strikingly effective in reducing the incidence of the disorder. Timely detection of venous thrombosis can be quite difficult; the first manifestation may be a fatal embolus. In most cases, however, venous thrombo-embolism can be recognized in advance of a major catastrophe. Modern methods of treatment are extremely effective in preventing deaths from embolism. In short, venous thrombo-embolism is hard to prevent, difficult to recognize, dangerous and yet responsive to treatment. Any such disease requires the physician's constant watchfulness. This review is a general summary of modern clinical experience with pulmonary embolism, as we interpret it.

ETIOLOGY

The primary cause of pulmonary embolization is the free-floating clot which is carried from the venous system or the right side of the heart into the pulmonary artery. The clot is usually bland, but on occasions may be septic. The various sites of thrombosis are the leg veins, femoral or iliac veins, pelvic veins, inferior vena cava, arm veins and the right auricle and ventricle. Although the exact frequency with which sites in the venous system are involved has varied in the experience of different authors, emboli originate in the pelvic, thigh and leg veins in most cases. Hunter *et al.* (21) in a study of 351 unselected autopsy cases, found that leg vein thrombi occurred in 53%. Of these people with leg vein thrombi, 21% had non-fatal pulmonary emboli and 5% had fatal pulmonary emboli. Of the 351 patients, only 11 had thrombi originating in other regions of the venous system than in the leg veins. In the past, the impression has been that in noncardiac patients 85–90% of the thrombi which yield pulmonary emboli originate in the deep veins of the lower leg, although the clot may extend to the thigh. More recently, McLachlin and Paterson (28) concluded from postmortem studies that in noncardiac patients 72% of the pulmonary emboli arise from the pelvic and thigh veins. In cardiac patients with pulmonary embolization, up to 25% of emboli may arise from the right side of the heart (4, 6, 15). In the same series, the leg veins were involved in between 32 and 48% of the cases and the pelvic veins in less than 10%. It should be emphasized that the arm veins are an infrequent site of thrombosis from which an embolus may arise.

Although there is difference of opinion among the various students of pulmonary embolization regarding the most important sites of origin of emboli, it is reasonable to conclude that in noncardiac patients the embolus arises from the lower half of the venous drainage of the body in nearly all cases. In cardiac patients, as high as 25% of the pulmonary emboli may originate in the right heart, but it should be noted that in many of these patients incomplete search of the pelvic and leg veins was carried out, or thrombi were also noted in the leg veins. The site of origin of the embolus is of particular importance when therapy is considered. It is also important to note that in the various autopsy and clinical surveys reported, the type of patient population as regards age, sex, disease state and type

of therapy all have a bearing on the experience of the authors.

The exact mechanism by which the original thrombus is formed in most patients is not well understood. Clinical experience indicates that certain events predispose patients to thrombo-embolism. These include operation, parturition, trauma to any part of the body and bed confinement. In addition, special kinds of disorders appear to contribute to the development of venous thrombosis. These include disease states or situations in which there is circulatory stasis, hemorrhage, shock, infection, malnutrition, anemia or dehydration. In cardiac patients in whom emboli arise from thrombi in the right side of the heart, myocardial damage, cardiac dilatation and cardiac arrhythmias are also important contributing factors. It is common, however, to find thrombo-embolic phenomena in patients who have had none of these predisposing or contributing factors.

The three principal factors that generally seem to be responsible for the formation of thrombi which may serve as the site for embolization to the lung are changes in the vein wall, slowing of the circulation and increased coagulability of the blood. Any of the three or a combination of the three may be involved in a particular patient. Whether the resultant thrombus represents phlebothrombosis or thrombophlebitis is a matter of terminology, decided by the intensity of the accompanying inflammatory reaction. It is widely thought that intense thrombophlebitis causes a close adherence of the thrombus to the vein wall, which makes embolism somewhat less likely than with phlebothrombosis. This is certainly true to the extent that superficial thrombophlebitis rarely causes significant pulmonary embolism.

Alteration of the vein wall has been implicated as important to the development of a thrombus. In the process which gives rise to embolization, however, the thrombus is notoriously friable and poorly attached to the vein wall, indicating that inflammation or injury to the endothelium is relatively inconspicuous, at least at the point where the embolus breaks off. This is the process that has been referred to as phlebothrombosis, in contrast to thrombophlebitis as outspoken inflammation of the vein wall. From pathologic studies of veins which were the site of thrombosis in patients with pulmonary embolization, Paterson and McLachlin (33) conclude that inflammatory reaction does not play a part in the process which gives rise to bland emboli. Although there is disagreement on the exact role of alteration of the endothelium of the vein in precipitating

thrombosis, it seems probable that in some cases endothelial damage results in the deposition of platelets and the formation of a clot. Where there is frank thrombophlebitis, thrombosis forms in the contralateral venous system or adjacent venous systems in many cases. Situations in which the vein wall may be injured to some degree include peripheral vascular disease which involves particularly the veins, such as thromboangiitis obliterans; trauma to the legs or pelvic region; surgery to the abdomen, pelvic region or legs; and pressure over a segment of the vein as with prolonged bed rest in one position or use of a truss or garter.

Retardation of venous flow favors the development of thrombosis by allowing stasis of blood in some channels or in small veins. The exact mechanism by which stasis initiates or aids thrombus formation is unsettled. Sludging of blood, accumulation of platelets on a pre-existing clot and accumulation of clotting factors on the surface of the initial clot at the site of endothelial alteration are possible modes of developing or propagating a thrombus in a region of slow flow. Disease states or conditions associated with venous stasis include immobility, as with bed rest or with cerebral vascular accidents; sitting with relative immobility of the legs, particularly with the legs in positions in which veins are partly or completely occluded; increased abdominal distention produced by obesity, pregnancy or abdominal binders; local constriction of the veins with garters or a truss; and varicosities. Derangement of cardiovascular function is also extremely important in slowing venous flow, and congestive heart failure is particularly important as a common factor in thrombo-embolic disease.

Stasis in the peripheral venous circulation is considered by most authorities as one of the most important causes of venous thrombosis. The return of the venous circulation to the right side of the heart is dependent on the force of the heart beat, contraction of muscles in the extremities and the aspirating action of the chest with respiration. It is adversely affected by increased viscosity of the blood, the effect of gravity on the return of blood from body regions below the heart and local venous obstruction. Alterations in these factors may induce stasis in the venous circulation and predispose to the formation of venous thrombosis. The various states associated clinically with venous thrombosis and pulmonary embolization, as listed above, usually involve impairment in one or more of these

factors which are responsible for the return of blood from the venous system to the right side of the heart.

Changes in blood composition may be a primary or predisposing factor in precipitating venous or right heart thrombosis. Alterations in composition which may be significant include platelet changes, increased red cell volume, abnormalities of the red cell, decreased plasma volume and abnormalities of plasma clotting factors. Specifically, various authors have suggested that increased fibrinogen or fibrinogen B levels, a decrease in blood antithrombin or alpha-tocopherol level, low fibrinolytic activity of the blood or an excess of platelets are the primary causes of thrombosis. Severe trauma, surgery, obstetric disorders, wound infection, advanced malignancy and blood dyscrasias are common examples of situations which may alter the blood in a manner that favors thrombosis. Polycythemia, dehydration and rapid diuresis in congestive heart failure apparently enhance thrombus formation because of a relative decrease in plasma volume and increase in blood viscosity. Once the initial clot is formed, changes in blood composition may be important in propagation of the clot and formation of additions to the thrombus.

The operation of the three primary factors previously discussed usually produces a bland venous thrombosis which is classified as phlebothrombosis. Subsequent to the development of the thrombus, there is a variable degree of reactive inflammation in and around the vein wall. The greater the degree of inflammation in the vein and surrounding lymphatics, the more organized the thrombus is likely to become and the more marked the symptoms related to the portion of the venous system involved. This latter situation is usually termed thrombophlebitis. Although it is often stated that the well-organized clot of thrombophlebitis is not likely to yield emboli, it should be emphasized that about one fourth to one third of patients with frank thrombophlebitis have also associated phlebothrombosis in the same venous system or in the contralateral venous system. Moreover, the distinction between the two processes is one of degree and both processes have some element of inflammation and a potentially friable clot associated with them.

The basic factors causing thrombus formation in the veins of the lower part of the body may also be important in thrombus formation in arm veins. In general, however, stasis is less important in formation of thrombi in arm veins, and trauma, irritation or injury to the vein wall are more significant. In

patients with cardiac disease in whom emboli arise from mural thrombi in the right heart, myocardial damage, arrhythmias, heart chamber dilatation or valve damage may be the initiating factors. Stasis of blood and alterations in blood composition are important in propagation of a friable clot in both of these situations.

Although pulmonary embolization is not common in healthy, ambulatory people, attention was particularly drawn to the occurrence of thrombo-embolism in this group by Homans (19). A surprising number of these patients have been observed in the past few years. This condition is distinguished by the following features: (1) It occurs almost without exception in young males, (2) two thirds of the patients have recurrent bouts of phlebitis which often have no predisposing or antecedent factors, (3) frequently the first episode is associated with prolonged sitting or mild trauma to the legs, (4) a history of phlebitis is often found in other members of the family and (5) eventually less than one tenth of these patients ever prove to have any of the disorders commonly associated with venous thromboembolism. Homans (20) and Petch (36) have described series of patients who have presented this type of venous thrombosis and pulmonary embolization. The following case report is an example of this syndrome.

CASE 1.—A 29-year-old male aircraft worker was first admitted to the Durham Veterans Administration Hospital in May, 1955. History showed that the patient had had a bout of "phlebitis" in 1950 following a night of sleep in a cramped position in the bunk of a trailer truck. When he awoke, his left thigh was swollen and painful. Twenty-four hours later he developed pleuritic chest pain and was hospitalized for 1½ months and treated with anticoagulant therapy and leg elevation.

In 1951, the patient had a sudden onset of pain in his right arm, with swelling of axillary and cervical lymph nodes. Some 24 hours later he had pleuritic chest pain with fever, but without cough or hemoptysis. At that time, he was hospitalized and an infiltrate was noted on the chest film. He was discharged 1½ months later.

Six months after the second episode, he awoke one morning to discover that the vessels of his right hand and wrist were tender and his right wrist was somewhat swollen. He was again hospitalized but had no pulmonary complications with his illness.

In 1955, following a 3-hour nap seated in his truck, pain in the left calf occurred, with swelling and a cord-like tenderness in the region. He was hospitalized but had no pulmonary complications. One month later, he experienced severe bilateral low chest pain, which migrated to the abdomen. With this, he had a slight cough, tempera-

ture elevation to 101 F., a feeling of faintness but no hemoptysis. His local physician made the diagnosis of pleurisy. He was then admitted to the Durham VA Hospital. After anticoagulant therapy and conservative management of his thrombophlebitis, the patient was discharged.

He was readmitted in January, 1958. Two weeks before admission, he had had a chill and left anterior chest pain, with a cough which was slightly productive of blood-streaked sputum. At the time of admission, he had the physical findings of left pleural effusion, and there was an increase in the circumference of the left leg as compared with the right. X-ray examination showed fluid in the left pleural space. Thoracentesis revealed a serosanguineous fluid and the patient was started on anticoagulant therapy. This has been continued as long-term treatment while the patient is out of the hospital. Inferior vena cava ligation was recommended but declined by the patient.

In most cases of pulmonary embolization, no factor can be identified as actually dislodging a portion of the thrombus. However, deep breathing, coughing and straining at stool frequently appear to be associated with pulmonary embolization.

This discussion is primarily concerned with pulmonary embolization in which a blood clot obstructs the pulmonary artery. It should be mentioned that other substances may embolize the lung and present a similar clinical picture. These materials include fat associated with bone fractures or other trauma, air from neck surgery, thoracentesis or rapid decompression, septic emboli, tumor and foreign bodies.

PATHOLOGY AND PATHOLOGIC PHYSIOLOGY

Emboli may block the main pulmonary artery and extend even into the outflow tract of the right ventricle. They may block arteries to lobes and over-ride arterial openings at major bifurcations. Usually, the emboli occur in smaller pulmonary arteries, are multiple and vary in age (4). The lower lobes are involved about 75% of the time (18). The relative incidence of small emboli as compared with large has been difficult to determine. Roe and Goldthwait (40) found that in 5,906 autopsies from 1931 to 1947, 4.3% of the patients demonstrated small incidental emboli, 2.7% had massive emboli and 0.9% had large emboli. It appears likely that even with large emboli, small fragments break off and lodge in smaller pulmonary vessels. It is also probable that most patients with pulmonary embolization have multiple emboli (4).

After lodgment of the embolus or emboli and obstruction of pulmonary blood flow, infarction of pulmonary tissue may or may not occur. The size of the vessel, the location of the vessel, pulmonary congestion or pulmonary infection and survival time of the patient are all factors involved in the development of infarction. Clinical observation has indicated that infarction following embolization usually occurs in patients who have had concomitant pulmonary congestion or edema. Hampton and Castleman (18) reviewed 370 cases of pulmonary embolism found at autopsy and noted that infarction had developed in 58% of postoperative patients with embolism, while infarction developed in 90% of cardiac patients with emboli. Experimentally, attempts to produce pulmonary infarcts with large or small emboli in healthy dogs have been unsuccessful. Dogs with distemper or acute pulmonary edema often have parenchymal changes characteristic of infarction (9, 39). In general, experimental work has suggested that infection, decreased aeration and congestion of the lung appear to be factors favoring pulmonary infarction.

During the first several hours after the emboli have lodged, no pathologic changes are observed in the lung. During the first 2 days after embolization, there is capillary congestion and diapedesis of red cells into the alveoli. This is followed by alveolar wall necrosis and red cell degeneration. The infarct usually extends to the pleural surface and may result in a serous or serosanguineous effusion in the pleural space. During the second week after embolization, organization occurs and healing progresses by fibrosis. The fibrotic reaction results in contraction, leaving a linear scar (18). Incomplete infarction in which there is no alveolar wall necrosis can heal by resolution instead of by organization. In this situation, no residual changes are observed in the lung.

Cavitation may occur in an infarct which results from a bland embolization (44). In a postmortem study, cavitation was observed 23 times in 550 cases of pulmonary infarction (25). Infection of the infarction is apparently almost always the cause of cavitation, but the commonest route of entrance of the infecting organisms has not been established.

Experimental evidence indicates that severe circulatory disturbances will occur if 60-85% of the pulmonary circulation is blocked off, and obstruction is generally fatal when it is 85-95% complete (16). With lesser degrees of obstruction there is an increase in pulmonary vascular resistance, and pulmonary artery and right ventricular pressures rise.

Circulatory and cardiac disturbances which occur with large pulmonary emboli may be due to mechanical interference with cardiac output, vascular reflexes, myocardial ischemia or hypoxia and arterial anoxemia. These factors may all contribute to, or be associated with, a fall in arterial blood pressure and the development of shock. Myocardial ischemia or hypoxia may be due to reduction in cardiac output, arterial anoxemia and possibly reflex vasoconstriction of the coronary arteries (46).

The pre-existing state of the circulation may also be important to heart function during acute embolization. In previously hypotensive animals, pulmonary embolization more frequently results in death than in normotensive animals (45). There is also evidence favoring and refuting the existence of pulmonocoronary reflexes, which have been held responsible for the sudden death observed in some patients with pulmonary embolism. Likewise, it has been stated that a small embolus may give rise to serious consequences by inducing reflex pulmonary vasoconstriction. The clinical evidence for this is most uncertain and animal experimentation does not provide firm support for reflex pulmonary vasoconstriction produced by embolization (24).

Recently, it has been suggested that humoral factors may produce or contribute to the production of cardiac, pulmonary and circulatory dysfunction in pulmonary embolization. Specifically, serotonin, which has been shown to be released from a blood clot or collection of platelets, has been found to produce in animals an increase in pulmonary vascular resistance diffusely through the lungs (42). It has been suggested that this substance may be responsible for some of the acute circulatory changes developing after pulmonary embolization.

Arterial anoxemia, usually moderate, has been observed in pulmonary embolization and infarction, but the pathologic physiology is not well understood. This subject is discussed under Signs and Symptoms (see p. 14).

SIGNS AND SYMPTOMS

Massive Embolization without Infarction

Immediate death may result from massive pulmonary embolization. Sudden severe dyspnea often heralds the onset of embolization. Momentarily before the respiratory distress there may be a short period of apnea. Often, severe, crushing substernal or generalized chest pain is noted. Sweating, pallor,

cyanosis, nausea, chilliness, abdominal discomfort, desire to defecate and extreme apprehension are frequently present. Mental symptoms, ocular palsies and convulsions may occur. When death results from massive embolism, it usually occurs within a matter of minutes but may be delayed for hours or even a day or two.

The physical findings in massive embolization without infarction are limited for the most part to the cardiovascular system and are primarily those of shock with acute pulmonary hypertension. Rapid, labored respirations, cyanosis and pallor are evident. The skin is moist and cold. The blood pressure is low or unobtainable and the pulse and respiratory rates are increased. Prominent pulsations may be noted over the pulmonic area and a shock can be palpated in this region. A loud pulmonic second sound, a systolic murmur and a gallop rhythm are commonly heard. The neck veins are distended, but in isolated episodes of embolism other evidences of right heart failure rarely have time to develop before death or improvement of the patient. When massive pulmonary embolization is fatal, it usually causes death from cardiovascular collapse before evidences of infarction have had time to develop.

Nonmassive Embolization without Infarction

Smaller pulmonary emboli or embolization without infarction may be overlooked unless a mild transient episode of syncope, breathlessness, an episode of palpitation or chest pain with a fall in blood pressure is correctly interpreted as caused by an embolus. This type of subclinical embolization apparently occurs frequently and may be suspected strongly when any of the above findings or symptoms occur in a patient who is bedridden, postoperative or who has some type of cardiac disease. This diagnosis should also be suspected in patients with the symptoms and signs of peripheral venous disease. On occasion, laboratory studies may help with the diagnosis.

Pulmonary Infarction

The signs and symptoms of pulmonary infarction are closely associated with those of embolism. Not only does infarction follow quickly after embolism, but fresh embolism may complicate the picture of a fully developed infarction. In addition,

certain symptoms such as chest pain and dyspnea occur in both conditions. For this reason, experienced clinicians, when describing the manifestations of pulmonary embolism, frequently do not trouble to distinguish between the signs and symptoms of embolism and those which are peculiar to infarction. For the less experienced student of the subject, however, such a differentiation can be extremely useful in keeping him abreast of an acute and changing clinical situation.

The cardinal symptoms of infarction are pleuritic pain, cough with bloody sputum and fever. Other symptoms which are frequently described, and which occur under somewhat special circumstances, are cyanosis, jaundice and pronounced dyspnea. Some of these will be discussed below in relation to the causative mechanisms, both in embolism and infarction.

Chest pain is frequent with an acute embolism of large size. This pain, or discomfort, has been described sometimes as a sensation of fullness or choking and sometimes as indistinguishable from the pain of angina or myocardial infarction. The origin of the pain is uncertain, but it may be caused by acute pulmonary hypertension or by myocardial ischemia. Unless a secondary myocardial infarction develops, this pain is not persistent. With the later formation of an infarct, pleuritic pain may occur. Pleuritic pain is characteristic of infarction.

Dyspnea can occur in association with both embolism and infarction. In acute embolism, the feeling of breathlessness is common. The origin of this sensation is obscure. It may be reflexly induced by acute pulmonary hypertension. It is reminiscent of the hyperventilation exhibited by people with chronic pulmonary hypertension during exercise, when there is an acute further increase in pulmonary arterial pressure. Dyspnea may also be intensified by the moderate arterial oxygen unsaturation which can occur with massive embolism. A degree of oxygen unsaturation which would be asymptomatic in a normal subject can intensify dyspnea in a person already short of breath. The dyspnea of severe exercise at high altitudes and the dyspnea of the orthopneic cardiac are examples of this intensifying effect of moderate oxygen lack in a patient already dyspneic for other reasons. Circulatory shock can also induce moderate hyperventilation, and this factor may be of minor additional importance. In pulmonary infarction, dyspnea is by no means invariable. By the time an infarct has developed, pulmonary hypertension and vascular insufficiency are usually less extreme. Cyanosis may still be present or may be intensified

if much atelectasis has occurred. For the most part, however, the association of dyspnea with an infarct depends on either restriction of chest motion by pleuritic pain or intensification of congestive heart failure in a person with independent cardiac disease.

Some investigators say that acute pulmonary embolism produces reflex bronchoconstriction (22). We have not observed clinical evidence of this in terms of the production of wheezing by massive embolism. In congestive heart failure in association with the subsequent infarction, as in acute congestive failure which develops on other grounds, wheezing respiration is common.

Although cyanosis is commonly observed in persons who have recently had a massive pulmonary embolus, there are surprisingly few data available on the arterial blood-oxygen saturation under these circumstances. The observations that have been made indicate only a moderate degree of arterial oxygen unsaturation, a value of 90% saturation being roughly representative. In such cases, cyanosis must be peripheral in origin, the result of marked reduction in the rate of blood flow through the skin. Such arterial oxygen unsaturation as occurs is probably the result, in most cases, of maldistribution of blood and gas in the lungs. In massive pulmonary embolism, much of the ventilation is distributed to lung regions which are not being perfused with blood, while the entire cardiac output may be restricted to a relatively small portion of the lung, where it is exposed to a relatively small fraction of the minute ventilation. Consequently, the blood must be less well aerated than normally. In some instances, a patent foramen ovale may permit shunting of blood from the right to the left atrium in patients with acute cor pulmonale and an elevated right atrial pressure. In an occasional patient, this mechanism could account for marked arterial oxygen unsaturation.

Hemoptysis occurs with infarction and is not part of the picture of acute embolism. Many patients, even those with large infarctions, do not have hemoptysis. Cough is quite frequent with infarction, and it may be productive of mucoid sputum which need not be blood-streaked.

A common indication of the occurrence of infarction, especially in a cardiac, is the unexplained appearance of moderate fever, tachycardia and sometimes tachypnea.

In cardiacs, jaundice sometimes appears after pulmonary infarction. This has been explained on the basis that a con-

gested and anoxic liver can not excrete with normal readiness the large amounts of bilirubin derived from the destruction of red cells in the infarct.

The physical signs of infarction are related primarily to the cardiopulmonary system. Most of the patients have some degree of tachycardia and increase in respiratory rate. Most appear apprehensive or anxious, particularly during the first day or two of their illness. Many, however, are relatively comfortable at the time they are first seen. Occasionally there will be cyanosis or jaundice.

Fever is a frequent finding and its severity probably depends on the extent of the infarction. No characteristic fever pattern is observed. Chills are usually not associated with this type of febrile illness. The temperature may occasionally be as high as 103-104 F. and remain elevated for 7-10 days. Longer temperature elevations may occur if abscess formation results at the site of infarction.

The physical findings in the chest depend on several factors which may be found singly or in combination. These are consolidation, atelectasis, pleural effusion and elevation of the diaphragms and restriction of chest motion.

Shortly after infarction, little may be found on examination of the chest and in some cases physical signs are minimal or absent during the entire course of the infarction. The following description applies to infarcts of considerable size. During the first 36-48 hours, decreased breath sounds may be heard over the area involved. Commonly, a pleural friction rub is noted. Splinting of the chest is frequent. Later, as signs of consolidation develop, the percussion note becomes less resonant and the breath sounds become bronchial in character. Because the lower lobes are involved most frequently, these changes are found at the bases of the lungs posteriorly and laterally. Elevation of the diaphragm on the left results in the physical finding of a tympanitic percussion note as high as the fourth interspace. Over this region, breath sounds are not heard, but bowel sounds may be audible. On the right, diaphragmatic elevation results in physical findings which cannot be distinguished from pleural effusion. The signs of pleural effusion are noted in about one fourth to one third of the cases. Decreased vocal fremitus, dullness to flatness on percussion and decreased breath and voice sounds indicate a sizable effusion. Tracheal shift can be observed in massive pleural effusion with infarction.

Pulmonary infarction may be mistaken for infectious pneu-

monitis. Repeated episodes may occur without the true nature of the illness being recognized. When venous thrombo-embolism appears in the course of another disorder, the most obvious manifestations may be overlooked or wrongly explained away unless the physician is alert to the possibility of the disease. The following case illustrates the occurrence of repeated infarctions which were mistaken for recurrent episodes of pneumonitis in a patient with acquired hemolytic anemia.

CASE 2.—A 59-year-old farm wife was admitted to the hospital with the complaints of progressive weakness and easy fatigability for at least 3 weeks. About 2 weeks before admission, she had begun to have some discomfort in the left leg and shortly thereafter developed tender, warm swelling along the inner portion of the left lower leg.

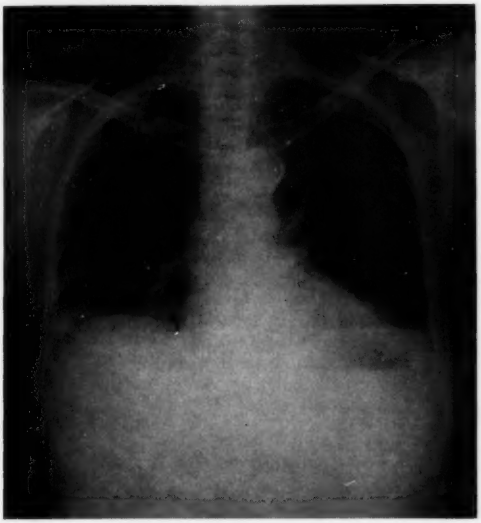
Physical examination showed a moderately obese, sallow, white female. The blood pressure was 128/82 mm. Hg. The optic fundi demonstrated several flame-shaped hemorrhages and cotton wool exudates. The chest was clear. The heart was not enlarged. The rhythm was regular. The aortic second sound was louder than the pulmonic. At the base, maximal in the aortic area, there was a grade II rather rough systolic murmur. On inspiration, the hepatic edge descended 3 cm. below the costal margin, and the spleen descended 5 cm. Over the course of the greater saphenous vein in the left lower leg, there was a firm, tender, warm thickening. There appeared to be some independent tenderness of the left calf. Homans' sign was positive on the left. There was a trace of edema in the left ankle.

The hemoglobin was 6.4 Gm.%, the red count 1.6 million and the hematocrit 19.6%. Reticulocytes were 39%. The white count was 7,400. Direct Coombs test was positive. A chest film and electrocardiogram showed no abnormalities. After additional studies, it was decided that she had an acquired hemolytic anemia, and prednisolone therapy was begun.

For the first week of her hospital stay, she had a low-grade fever, rarely exceeding 101 F. Thereafter, fever subsided. The signs of acute thrombophlebitis disappeared. On the 18th hospital day, she was discharged for a trial of prednisolone therapy.

Two weeks after discharge, it was decided that she was not having a satisfactory hematologic response to steroid therapy, and she was readmitted for splenectomy. There had been no further complaints related to the legs. Examination showed slight bilateral pretibial and ankle edema. There was a daily temperature elevation on the order of 100-101 F. A chest film showed no abnormality. On the 5th hospital day, a splenectomy was performed. Postoperatively she continued to run a low-grade fever. On the 10th hospital day an area of acute superficial thrombophlebitis appeared on the left lower medial leg. A chest roentgenogram on the 11th day showed linear densities at both bases, more on the right, and some patchy areas of increased

density at the right base. On physical examination, there was some dullness at the right base posteriorly, and the breath sounds were bronchial in character and decreased in intensity. She was thought to have pneumonia. Antibiotics were administered but fever continued for the next 4 or 5 days. On the 14th hospital day, moderate pitting edema of both legs was observed, there was some superficial venous engorgement and the right thigh was found to be 2 cm. larger



Roentgenogram of Case 2 during the 4th hospital admission. There are linear densities at both bases, probably "plate-like atelectasis," and clouding in both costophrenic angles and in the periphery of the right mid-lung field.

around than the left. Heparin was administered, followed by Dicumarol®, and this anticoagulant treatment was continued until discharge. After a few days of complete bed rest, and the administration of anticoagulants and antibiotics, the local manifestations of thrombophlebitis cleared up and fever subsided. On the 20th hospital day, a chest film showed that the linear densities at the left base had disappeared, and there was partial clearing of the density at the right base. She was discharged on the 22d hospital day, still taking prednisolone but no anticoagulants.

For the next few weeks she got along well except for the development and persistence of marked pitting edema of the legs. The hemoglobin rose to 12.9 Gm. Five weeks after discharge, she had a fever of 101 F., pleuritic right chest pain and a friction rub in the right lateral chest. She was given penicillin and gradually improved. Ten days later, however, she reappeared, complaining of a recurrence of fever of 101 F. and pleuritic pain in the left chest. Physical examination revealed a few rales at the right base, and a chest film was reported to show bilateral basal pneumonitis and two small areas of increased density in the right upper lung field. On this occasion, she was given tetracycline. She remained at home in bed for 10 days and then returned to the hospital complaining of severe pain in the legs on walking. There was bilateral ankle edema, increased warmth of both legs and a positive Homan's sign on the right. There were crepitant rales and dullness at the right base.

She was readmitted to the hospital with a diagnosis of thrombophlebitis and pulmonary infarction. Again, she ran a low-grade fever. There was disagreement as to diagnosis, and she was discharged 4 days later.

One month later, she returned for her 4th hospital admission in 4 months. She had a fever of 101 F., tender swelling of the left leg and thigh and a history of pain on walking which had been progressively more severe for the past 3 weeks. A chest film (see illustration) showed linear densities at both bases, and clouding in both costophrenic angles and in the right mid-lung field. On this occasion, there was general agreement that she was having recurrent pulmonary infarction. She refused caval ligation and plans were made for long-term anticoagulant therapy.

Peripheral Venous Thrombosis and Thrombophlebitis

It is well recognized that fatal pulmonary emboli may be cast off by a peripheral venous thrombus which has given no clinical evidence of its presence. Even on services which are actively studying the problems of pulmonary embolism and routinely searching for venous thrombosis, about half of the cases with major embolism show no signs of peripheral thrombosis at the time of the first embolic episode (1, 6, 12). This episode may be fatal. In the experience of the Mayo Clinic with postoperative thrombo-embolism, the first recognized episode of embolism was fatal in 24.4% of the cases (2). Venous thrombosis calls attention to itself by the signs and symptoms caused by the associated inflammation and obstruction to venous outflow. In general, the disorder is easier to detect in superficial veins than in deep veins. Even with large thrombi, inflamma-

tion and obstruction may be slight, and if the affected veins are deeply situated, the thrombus can escape diligent search.

Superficial thrombophlebitis offers no diagnostic difficulty. The familiar picture is that of a tender, reddened, firm, cord-like swelling. Superficial veins rarely seem to yield emboli of consequence, but the spontaneous appearance of superficial thrombophlebitis should suggest the possibility of thrombi in larger, deep veins.

Femoro-iliac thrombophlebitis may make its presence known unequivocally by swelling of the leg and thigh, but it may also occur in the absence of edema or other evidence of thrombosis. Pain in the thigh and inguinal region is frequent and may be quite severe. Tenderness may be elicited over the femoral vein. Arterial spasm sometimes occurs in association with acute femoro-iliac thrombophlebitis, causing confusion as to whether the arterial or the venous system is primarily involved. Bluish discoloration of the extremity, swelling and distended superficial veins are frequently present in femoro-iliac thrombophlebitis and are characteristic of venous rather than arterial obstruction (1).

Thrombosis in the deep veins of the lower leg may also be quite silent. Calf pain or lameness on walking, slight ankle swelling or possibly some duskiness of the foot may draw attention to this region (19). Homan's sign is often present in cases of deep calf vein thrombosis. This consists of the occurrence of discomfort back of the upper calf and knee when the Achilles tendon is stretched by forced, passive, dorsiflexion of the foot. There is often no definite tenderness on manually squeezing the calf, but it is said that increased calf tenderness can sometimes be brought out by inflating a sphygmomanometer cuff around the calf (26). When the cuff is inflated for 10-15 seconds, the normal subject is unlikely to experience pain unless the pressure exceeds 180 mm. Hg. Patients with deep calf vein thrombosis may complain of pain at pressures of 60-150 mm. Hg.

Probably the most valuable single diagnostic procedure is routine, repeated measurements of the circumference of leg and thigh in patients with conditions which predispose to the development of thrombosis.

Systemic evidence of thrombosis such as fever and leukocytosis seems largely to depend on the extent and intensity of the inflammatory reaction.

LABORATORY FINDINGS

The laboratory findings in persons with pulmonary embolism and infarction are generally nonspecific. Even so, they can be helpful in distinguishing between this condition and others with which it may be confused, especially pneumonia and myocardial infarction.

There is great need for a test to indicate the existence of fresh intravascular thrombosis or of an abnormal clotting tendency. It is plain that such a tendency exists in certain people without known causes, and that it occurs to some extent in many persons under special circumstances, such as postoperative or postpartum states (53). To date, however, no satisfactory laboratory test for this clotting tendency has been reported. In the postoperative state, the clotting mechanism has been studied extensively and certain changes have been found. These changes do not seem entirely consistent (51). For example, there is said to occur at some time in the first postoperative week, thrombocytopenia and a decrease in prothrombin conversion accelerator factors. However, it is also found that the coagulation time of whole blood is shortened, prothrombin consumption is increased and antithrombin activity is decreased. In the second week, thrombocytosis occurs and prothrombin conversion accelerators return to normal, while prothrombin consumption and antithrombin activity also become normal. The fibrinogen concentration is elevated to some extent from the middle of the first postoperative week to the middle of the second week. For comparison, about one quarter of postoperative thrombo-embolic disorders become apparent during the first 8 days after operation, one half during the 9th-14th days and the remainder thereafter (2). The whole problem of pulmonary embolism would be enormously simplified by a test that could reflect this increased clotting tendency which is so painfully evident on clinical grounds.

In uncomplicated pulmonary embolism of sufficient size to produce an obvious systemic reaction, with or without subsequent pulmonary infarction, routine laboratory procedures are of little help. There is often a moderate leukocytosis. The bloody sputum of an infarct contains at first few leukocytes or bacteria, but this is also true of many viral and even some bacterial pneumonias. A sanguineous pleural effusion may occur; in patients with congestive heart failure, this finding suggests pulmonary infarction.

Patients with chronic congestive failure and impaired hepatic function sometimes become jaundiced a few days after the occurrence of pulmonary infarction. The increased bilirubin is primarily indirect-reacting. The usual explanation for this phenomenon is that a liver which is functionally impaired by the ischemia of congestive failure cannot readily excrete the extra load of billirubin derived from the breakdown of a sizable pulmonary infarct.

Because of the need to differentiate between pulmonary embolism and myocardial infarction, studies have been made of the changes in serum glutamic-oxalacetic transaminase (SGOT) levels after pulmonary embolism (17, 30, 31). This enzyme, which is concerned with transamination between aspartic and alpha-keto glutaric acids, is present in high concentration in heart muscle, and it has been found that the serum concentration of SGOT rises markedly shortly after a myocardial infarction, reaching a peak level in 24-48 hours and generally returning to normal in less than a week. In the lung, SGOT concentration is low. In about two thirds of patients with pulmonary infarction, an elevation in SGOT has been found (31), but the increase was greatest, on the average, 5 days after the disorder became clinically apparent, and the peak values were low compared with those after myocardial infarction. SGOT elevations after pulmonary infarction have been said to occur only in patients with functional impairment of the liver (31). Patients with pulmonary embolism unaccompanied by infarction show little or no increase in SGOT. The test should be of considerable assistance in the occasional case where differentiation of pulmonary embolism and myocardial infarction is difficult. In addition, serial determinations could be valuable in detecting the development of myocardial infarction as a complication of pulmonary embolism in patients with pre-existing coronary artery disease.

Large pulmonary emboli often cause electrocardiographic changes. These are quite variable, but some generalizations can be made (7, 27, 37, 43). Massive pulmonary embolization may occur without producing an abnormal electrocardiogram. When ECG changes occur, some abnormalities are usually present within an hour after the onset of symptoms. Abnormalities are often transient, although some of them may persist for weeks. The ECG picture may be complicated by the development of coronary insufficiency or myocardial infarction, especially when

pulmonary embolization causes prolonged systemic hypotension in middle-aged or elderly persons.

The classic ECG pattern of acute cor pulmonale described by McGinn and White (27) occurs in only about 10% of patients with clinically apparent pulmonary embolism (7, 43). This pattern, the "S1, Q3, T3 pattern," consists of the appearance or exaggeration of an S wave in lead I, the appearance or exaggeration of a Q wave in III, and an inversion of T III, or a deepening if it is already inverted. Also described originally was a low take-off of S-T I, a gradual "staircase" ascent of S-T II and an upward bowing of S-T III. This picture, it is apparent, closely resembles that of a posterior myocardial infarction. In the precordial leads, there may be inversion of T waves over the right ventricle, a finding which is not usual in posterior infarction. In further differentiation from posterior infarction, it is stated that aVF is nearly always normal in pulmonary embolism. In the precordial leads, the QRS "transitional zone" may be shifted leftward. Transient right bundle branch block occasionally develops. There may be paroxysmal arrhythmias, of which auricular fibrillation is the most usual. Other less-well-defined alterations in the ECG have been described following pulmonary embolism, and are usually classified as "nonspecific changes." To some extent, these are characterized by a common tendency to be transient.

Roentgenograms of the chest show few changes in cases of pulmonary embolism without infarction. With large emboli, there may be evident a region of diminished density corresponding to the region of decreased vascularity (54). This clear region is more readily apparent in cardiac patients with pulmonary congestion elsewhere in the lung fields. In patients who recover without infarction, gradual revascularization of the ischemic region occurs with restoration of the normal density.

Our understanding of the roentgenographic appearance of pulmonary infarction has been aided particularly by the study of Hampton and Castleman (18), who correlated postmortem roentgenograms with autopsy findings. The roentgen shadow of an infarct does not usually begin to develop until at least 12-24 hours after the apparent embolization. In a previously normal lung, the infarct is usually "incomplete" in that it does not proceed to necrosis of the alveolar walls, and the corresponding roentgen shadow may disappear completely within a few days. When there is much necrosis of alveolar walls, the shadow may persist for weeks, shrinking and developing a

more distinct border as fibrosis occurs around the periphery. In such a case, healing often leaves a dense, linear scar which may be confused with interlobar pleuritis or atelectasis (14). About three quarters of infarcts occur in the lower lobes, more commonly on the right. These shadows are always in contact with a pleural surface, costal, diaphragmatic, mediastinal or interlobar and they often involve two pleural surfaces, as in the common location in the costophrenic angle. The long axis of the infarct lies parallel to the pleural surface which it mainly involves. The shape of infarcts is quite irregular, and is determined to a considerable extent by the shape of the lung region in which they occur. They are often hemispherical or shaped like half a spindle. When an infarct does assume a pyramidal shape, the aspect toward the hilum is rounded rather than sharply angular, because the infarcted region stops short of the point at which the artery is actually obstructed. Unusual shapes, such as circular shadows, may be produced by the overlap of two infarcts, seen in a particular projection. Pleural effusion often develops. This was present at death in 40% of the cases of Hampton and Castleman, but they concluded that there was good evidence for causal relationship between infarction and effusion in only 13%. The reduction in chest motion consequent on infarction is responsible for additional roentgenographic findings (53). These include restricted diaphragmatic mobility on the affected side, elevation of the diaphragm, a shortening of the distance between the dome of the diaphragm and the horizontal interlobar fissure line and areas of plate-like atelectasis. The latter occur in the lower lobes and appear to result from obstruction of bronchi by mucus accumulation in the dependent portions of a relatively immobile lung.

Cases of repeated embolization leading to chronic cor pulmonale may demonstrate the combination of a prominent pulmonary conus and prominent hilar shadows with abnormally clear lung fields.

THERAPY

Much attention has been devoted to the prophylaxis of thrombo-embolic disease. In those special situations in which the need for a vigorous approach is obvious from the beginning, such as myocardial infarction or the actual occurrence of nonfatal pulmonary embolism, modern treatment methods

are valuable in preventing subsequent thrombo-embolic disease. However, little demonstrable success has resulted from the use of the conventional prophylactic measures which have been applied in those situations in which thrombosis and embolism characteristically occur, but where the patient shows no evidence of the disorder (13, 38, 40). These situations include, for surgical conditions, the period immediately after operations, delivery or trauma and, for medical conditions, congestive heart failure and prolonged debilitating illness. Prophylactic measures have included bed exercises, early ambulation, use of elastic bandages on the legs and superficial femoral vein ligation in selected patients. These measures have not significantly reduced deaths from pulmonary embolism (40). The problem in prophylaxis is posed by the circumstance that those measures which can be applied widely are relatively ineffective, while those known to be effective are too rigorous for general application. The problem could be resolved by the discovery of a reliable test for the thrombotic tendency, or of an effective and innocuous prophylactic measure. Meanwhile, the best safeguard against fatal pulmonary embolism is probably careful, repeated, routine examination for early signs of thrombo-embolic disease in patients with the known predisposing disorders. In addition, the routine prophylactic measures already mentioned are certainly benign and may be of value in some cases.

The emergency treatment of patients with acute circulatory insufficiency from massive pulmonary embolism is also unsatisfactory. Contributions to this problem have been made largely by de Takats and Jesser (22, 47), who have suggested the use of oxygen and intravenous atropine (1 mg.) and papaverine (30 mg.). The use of atropine and papaverine is based on the belief that pulmonary embolization triggers reflex bronchoconstriction and constriction of the coronary arteries, and possibly other deleterious vasomotor reflexes. Atropine is used to block parasympathomimetic impulses and papaverine is intended to relax smooth muscle in vessel walls and in bronchi. The existence of specific reflexes affecting bronchi and coronary arteries and triggered directly by a pulmonary embolus is a controversial subject. We believe that the use of oxygen is advisable when shock or cyanosis is present, and that atropine is harmless even though its benefits may be debated. Our personal experience with papaverine, admittedly limited, has not been encouraging. Its hypotensive effect, in a patient who is

already in a precarious circulatory state, can be alarming and in some cases definitely harmful. In using these drugs, the physician should be aware that there is some uncertainty as to their efficacy, and he should be alert to their possible deleterious effects.

In venous thrombosis, with or without pulmonary embolism, therapy is directed toward preventing further thrombosis and embolism until the abnormal clotting tendency has disappeared. The two principal means used for this purpose are venous ligation and anticoagulant therapy, separately or in combination. Today, the general tendency is to depend, somewhat more heavily than in the past, on anticoagulant therapy and less on venous ligation.

Several excellent articles on the use of anticoagulant therapy in venous thrombo-embolism have appeared recently, notably those of Crane (12) and of Anlyan and Hart (1). The latter authors use somewhat larger doses of anticoagulants over a longer period. After obtaining a Lee-White clotting time and a one-stage prothrombin time, they customarily administer 75 mg. of heparin intravenously and then continue with 50 mg. of concentrated aqueous heparin subcutaneously every 4 hours. The clotting time is checked once a day, 3½ hours after the most recent dose, and if the clotting time in the third tube is greater than 25 minutes, the dose is reduced. With this dosage scheme, the peak clotting time usually lies between 30 and 60 minutes. In the schedule of Crane, heparin is given subcutaneously every 6 hours in doses of 50-75 mg. and daily clotting times are done 5 hours after the most recent dose. If the time is greater than 20 minutes, the next dose is reduced or omitted. For the first day or two, Crane recommends that the clotting time be measured 2 hours after the most recent dose, when it should be in the vicinity of 25-40 minutes. In his experience, refractoriness to heparin may be associated with widespread or continuing thrombosis. Crane continues heparin therapy for 6-10 days. Anlyan and Hart begin Dicumarol® on the 7th day of therapy. When the prothrombin time has fallen below 30% of normal, heparin is discontinued. Dicumarol® therapy is continued for 4-6 weeks.

As an adjuvant to anticoagulant therapy, absolute bed rest should be imposed until there has been no evidence of further thrombo-embolism for at least 2 weeks. For several weeks thereafter, prolonged standing or sitting with the feet in a dependent position should be prohibited. During the period of bed rest,

venous stasis in the legs can be minimized by elevating the foot of the bed several inches and by the use of elastic bandages from the ankle to groin. The patient should be carefully observed for evidence of recurrent thrombo-embolism in the period immediately following cessation of anticoagulant therapy.

Contraindications to anticoagulant therapy include the presence of a bleeding lesion, severe hepatic or renal impairment, a pre-existing derangement of the clotting mechanism and recent surgical procedures in certain body regions, especially the central nervous system, joints and genitourinary tract. Once a patient is on anticoagulant therapy, procedures such as lumbar puncture and paravertebral block should not be carried out. In the event of bleeding complications, intravenous protamine in doses up to 50 mg. is an effective antiheparin agent. Vitamin K_1, intravenously or orally in doses of 10-50 mg., is effective against Dicumarol® but requires several hours for full action. Where greater speed of response is essential, transfusions of fresh blood will meet the need.

In a series of 391 cases of venous thrombo-embolism treated with heparin, Crane (12) reported significant bleeding in 3.3% and fatal hemorrhage in 2 cases (0.5%). In this series, there were 4 deaths from pulmonary embolism. Defining therapeutic failure as further thrombosis or embolism during therapy or within 60 days of the cessation of therapy, he reported a failure rate of 11.3%. Most of these patients were surgical cases, in whom the tendency to thrombo-embolism is generally less persistent than in cardiacs or patients with chronic debilitating disease. When thrombo-embolism persists despite anticoagulant therapy, venous ligation is usually advisable.

Venous ligation as a primary procedure has had strong advocates (5, 6). Crane (12) suggests that the results of this procedure are about the same as those of anticoagulant therapy in comparable cases. The advocates of venous ligation generally believe that most emboli arise from the leg veins at such a level that bilateral interruption of the superficial femoral veins, or possibly the common femoral veins, constitutes a safeguard which is usually effective. This view has been contested by McLachlin and Paterson (28), who concluded on the basis of extensive postmortem dissections of the venous system in a series of 100 unselected males, 34 of whom demonstrated gross venous thrombosis, that superficial femoral ligation would have protected less than half of the cases from pulmonary embolism.

Anlyan and Hart also question the advisability of femoral vein ligation as a primary therapeutic procedure.

The great uncertainty attending venous ligation is the question of whether all potential emboli are situated distal to the site of ligation. Even when this is the case at the time of operation, there remains the possibility that a patient with a thrombotic tendency may later form new potential emboli in a portion of the venous system which is not blocked by the ligation. For these reasons, ligation of the inferior vena cava distal to the renal veins has been performed in selected cases more and more frequently in recent years (23, 34, 41, 49, 55). This procedure protects against emboli from the pelvic and leg veins, and there is little tendency to form thrombi proximal to the site of ligation. However, the procedure is a major operation. Undesirable sequelae, such as persistent edema, ulceration, dermatitis and leg pain both at rest and during activity have been reported to occur to a significant extent in at least half of the patients followed for several years. Because of these problems, there is often considerable reluctance to carry out the procedure. The operation may first be rejected when it should be done because the patient does not seem ill enough to warrant the risk of the sequelae. It may then be rejected at a later date because the patient has become too ill to withstand a major operation. Actually, many of the sequelae are those which might well have resulted from pre-existing thrombophlebitis quite apart from the operation (23, 34, 55). In many cases, there are no significant after-effects. In the over-all view, however, it is almost certain that the procedure must produce some sequelae beyond the phlebitic disease alone (41). It is now generally conceded that this operation should not be used prophylactically but should be reserved for the patient in whom other measures have failed to control progressive venous thromboembolism. In such circumstances, it can be lifesaving. The operation should be respected but not feared unduly. Mention should also be made of the classic indication for the procedure, which is septic pelvic thrombophlebitis.

In summary, the principal therapeutic reliance in venous thrombo-embolism is presently placed on venous ligation and the use of anticoagulant drugs. There is still considerable difference of opinion as to how these measures should be used, but there appears to be a growing tendency to depend largely on anticoagulant drugs and to emphasize heparin in the early stages of treatment. Venous ligation, especially of the inferior

cava, is a valuable procedure for those cases in which anticoagulant therapy is contraindicated or proves to be ineffective.

The intravenous administration of fibrinolytic drugs with the object of dissolving intravascular clots offers great promise for the future, but is still in an experimental stage.

Antibiotics are usually administered to patients with pulmonary infarction, primarily for two reasons. First, they protect against the risk, admittedly slight, that the infarct might become secondarily infected. Secondly, they are often given to be on the safe side in situations in which it is impossible to differentiate firmly between infectious pneumonitis and infarction.

REPEATED EMBOLIZATION AND CHRONIC COR PULMONALE

After nonfatal embolism in man, the clinical evidence of pulmonary vascular obstruction usually disappears completely. Correspondingly, it is reported that sizable emboli produced experimentally in the dog will fragment, lyse and ultimately disappear completely within 2-4 weeks (52). In exceptional human cases, however, repeated and extensive pulmonary embolism, which may be clinically unrecognized, can produce chronic, high-grade pulmonary vascular obstruction and pulmonary hypertension with the development of cor pulmonale and right heart failure (8, 32, 35). A similar situation has been produced experimentally in rabbits by the repeated injection of minute autogenous blood clots (3). In both rabbit and man, concentric arteriolosclerosis appears, as well as the asymmetric lesions which are easily recognizable as organized clot. Although this situation is unusual, it is being reported with increasing frequency. Since timely recognition and adequate treatment can prevent a fatal outcome, the disorder is important to the physician despite its rarity.

The condition occurs with roughly equal frequency in men and women. Most of the patients have been middle-aged. In most cases, the thigh and leg veins have given rise to the emboli but apparently mural thrombi of the right heart can be responsible (32). It is evident from some case histories that venous thrombo-embolism may occur intermittently over a period of years before death from cor pulmonale. In other cases, the span of the disease appears to be only a few weeks. There may be no history suggesting peripheral thrombosis or thrombo-

phlebitis. Occasionally, there is a history of repeated episodes of acute respiratory disorder diagnosed as pneumonia or pneumonitis. These evidently represent unrecognized infarctions. The clinical episodes are similar to those which have been reported in patients with the sickle state who are developing cor pulmonale (29).

Progressive dyspnea, present at first only on exertion, is the most prominent symptom. For reasons not altogether clear, patients with pulmonary arterial hypertension have an extremely high exertional breathing requirement. During exercise, they may easily have twice the normal amount of minute ventilation for a given rate of oxygen consumption. This characteristic response to exercise appears to be primarily responsible for exertional dyspnea in these patients. With the appearance of congestive failure, orthopnea develops. Interestingly, at this stage paroxysmal nocturnal dyspnea is a common symptom, even though pulmonary vascular congestion is not usually evident, either on physical examination or by roentgenogram. Cough occurs frequently, often with blood-streaked sputum. Chest pain is a common complaint. This may be pleuritic and presumably caused by a pulmonary infarction. Occasionally, pain occurs in the anterior chest on exertion and is relieved by rest. Exertional syncope is a characteristic and frequent symptom, especially in patients who are trying to maintain a physically active life despite growing disability. This resembles the exertional syncope of aortic stenosis in that it tends to occur particularly in patients who find themselves overextended physically by a situation beyond their control, as in walking on a treadmill. Cyanosis, usually episodic, is often observed. In 3 cases reported by Owen *et al.* (32) as demonstrating cyanosis at times, the arterial blood-oxygen saturation was found to be between 92 and 93.4%. This level of arterial saturation at rest is also usual in our experience. Lower values are sometimes found. In addition, it is not unusual to find a pronounced drop in arterial blood-oxygen saturation during exercise in these patients. Parenthetically, it may be noted that this is part of the reason for exertional overbreathing in some cases; but exertional overbreathing also occurs in patients with pulmonary arterial hypertension whose arterial blood-oxygen saturation remains within normal limits during exertion. The exertional drop in arterial blood-oxygen in these cases probably depends in part on maldistribution of blood and air in the lung, so that the regions which are being perfused are

relatively underventilated, and in part on the greatly reduced pulmonary diffusing capacity for oxygen. As noted earlier, cyanosis may also be occasioned by a right-to-left shunt through a patent foramen ovale. There remains, however, a group of patients who demonstrate episodic cyanosis, sometimes in association with impending syncope, but who show at subsequent autopsy no apparent defect through which a right-to-left shunt might pass. In these cases, cyanosis may depend on peripheral mechanisms, primarily slow blood flow through skin vessels. There is no tendency to retain carbon dioxide; in fact the CO_2-combining capacity may be moderately reduced. On exertion, there may be mild respiratory alkalosis due to overbreathing. Finally, easy fatigability is a most prominent symptom.

In late stages, these patients present the classic signs of right heart failure: dependent edema, ascites, hepatomegaly often with mild splenomegaly and distended neck veins, which may show marked pulsation in patients with functional tricuspid insufficiency. However, before this, they almost always present more specific signs, related to severe pulmonary hypertension. The pulmonic second sound is usually markedly accentuated and is often doubled. A corresponding pulmonic shock is often felt. In addition, there is frequently a visible and palpable systolic heave in the second and third interspaces along the left sternal border, owing to dilatation of the outflow tract of the right ventricle. In the pulmonic area, a grade III to IV systolic murmur of rough quality is sometimes present, and a blowing pulmonic diastolic murmur is occasionally heard. There may be a gallop rhythm, usually maximal in intensity along the left sternal border.

The electrocardiogram usually, but by no means invariably, demonstrates abnormalities. These include right ventricular hypertrophy, complete or incomplete right bundle branch block and T wave abnormalities over the right ventricle. A "P-pulmonale," i.e. a tall peaked P wave in leads II, III and aVF, indicating right auricular hypertrophy, is also a common finding. Arrhythmias are uncommon.

Roentgenograms present a combination of dilation of the right ventricular outflow tract and the hilar arteries, together with abnormally clear peripheral lung fields. Pulmonary arteriograms may show irregularities in blood distribution through the lung.

Therapy is directed toward preventing further embolization.

Anticoagulant therapy and caval ligation are the procedures on which reliance must principally be placed.

PULMONARY INFARCTION AND CONGESTIVE HEART FAILURE

Venous thrombo-embolism is especially prone to occur in persons who are in congestive heart failure or verging on failure, and pulmonary emboli often produce infarction in these people. For reasons still obscure, pulmonary infarction has a great tendency to precipitate frank congestive heart failure in compensated cardiacs or to make pre-existing failure much more severe. In most of these cases, there is no clinical evidence of peripheral thrombophlebitis. Infarction may occur in definite episodes, sometimes mistaken for infectious pneumonitis. An attack of this kind usually begins with unexplained tachycardia, fever and worsening of the symptoms of congestive failure. When hemoptysis and pleurisy follow in a day or two, and jaundice perhaps 4 or 5 days later, the nature of the illness is obvious. However, pulmonary infarction may also occur in repeated small episodes which produce chronic failure without the development of the classic signs and symptoms of infarction. The resultant chronic failure may be ascribed mistakenly to rheumatic or other chronic myocarditis, to masked hyperthyroidism or to myocardial exhaustion resulting from long-standing valvular disease. Tench (48) has pointed out that such patients may easily be overtreated in an attempt to control their failure by conventional means, so that they present a triad of tachycardia, digitalis toxicity and mercurial-fast edema. Patients with advanced mitral disease are especially prone to repeated infarction.

Without effective therapy, this combination of congestive heart failure and repeated pulmonary infarction has a high mortality rate (7). Until recent years, therapy was not sufficiently effective to influence appreciably the course of the syndrome, and there was a general impression that pulmonary infarction was simply a common terminal complication in progressive, fatal congestive heart failure which had developed independently of infarction. It is now appreciated that pulmonary infarction, apparent or inapparent, is often the proximate cause of the failure and that the downhill course can be reversed by preventing further infarction.

The mainstay of therapy in these patients is the use of

anticoagulant drugs, primarily Dicumarol® or its congeners. In some cases, however, anticoagulant drugs prove ineffective. Under these circumstances, ligation of the inferior vena cava can be a lifesaving procedure. Obviously, caval ligation cannot be effective in that minority group whose emboli are deriving from the heart or from some other site proximal to the ligature. The operation often appears formidable in a sick cardiac, but it must be remembered that the untreated disease has an extremely high mortality rate. The late effects of caval ligation are not unduly severe in cardiacs. Cossio reported that over half of a series of cardiac patients who had edema before ligation were relieved of edema after the operation (10). He reports an operative mortality of 6% (11), which is favorable considering the risk involved in allowing embolization to continue.

The following case illustrates the syndrome of recurrent pulmonary infarction in a patient with mitral disease, persisting despite anticoagulant therapy, and successfully treated by inferior caval ligation.

CASE 3.—A 41-year-old farmer had been generally well and had no history suggesting rheumatic fever or venous thrombo-embolism until 4 years before his first admission to Duke Hospital. At that time, he became ill with pleuritic pain followed by hemoptysis and by exertional dyspnea, paroxysmal nocturnal dyspnea and ankle edema. He was hospitalized elsewhere, a diagnosis of mitral stenosis was made and he soon regained compensation on digitalis and sodium restriction. Three months before admission, there was a similar episode, and he was hospitalized for a month elsewhere. Dicumarol® was given, since he appeared to be having repeated infarctions. Congestive heart failure cleared and he was discharged, still taking Dicumarol®. He did fairly well until 10 days before admission when he became markedly dyspneic again. Three days before admission, a chest film showed a new infiltrate in the left lung, there was a friction rub in the right anterior chest and he appeared slightly icteric.

Physical examination showed a thin, orthopneic male. The blood pressure was 120/70 mm. Hg. The apical heart rate was 130 and the rhythm was totally irregular. There were basal rales, scattered expiratory wheezes and a friction rub in the right anterior chest. The heart was moderately enlarged to the left. The apical first sound was loud and snapping, and the pulmonic second sound was accentuated and split. There was a grade I apical systolic murmur. At the apex, a faint rumbling mid-diastolic murmur was intermittently heard. The hepatic edge was felt 4 cm. below the costal margin. There was no ankle edema.

Fluoroscopy and films showed prominence of the pulmonary conus and the hilar vessels. The left atrium was enlarged. There was calcification in the mitral valve area. The left diaphragm was moderately elevated and there was an infiltrate in the left mid-lung field, which slowly cleared over several weeks. ECG showed auricular fibrillation and right ventricular hypertrophy.

He was hospitalized for 4 weeks. He had a mild fever which gradually subsided during the first 3 weeks. He was maintained on Dicumarol®, with a prothrombin level between 10 and 20% of normal. With adequate digitalization and a low sodium diet he lost 8 pounds. He was discharged to return in 4 weeks for a mitral valvuloplasty. Dicumarol® was continued.

Three weeks after discharge, he returned with cough, purulent sputum, chilly sensations and a mild fever. He was again orthopneic, but there was no ankle edema. Shortly after admission, he began to cough up bloody sputum. A friction rub appeared at the left base. A chest film showed some clearing of the old density, but there were new shadows in the periphery of the left mid-lung field and at the right base. Tachycardia and low-grade fever, which were present on admission, gradually subsided over the next 3 weeks, but 4 weeks after admission he had another episode of pleurisy and hemotysis. A few days later, ligation of the inferior vena cava was done. The postoperative course was uneventful, and he was discharged on a low-sodium diet and digitalis with instructions to wear elastic stockings.

For the first month, there was considerable leg edema, but thereafter he was edema-free even though he soon abandoned salt restriction. He complained of some "dead aching" in the legs, but discomfort was not severe. He still had exertional dyspnea to a degree which prevented working, but he stated that he felt better than at any time in 4 years. Six months after caval ligation, he was readmitted for study and valvuloplasty.

Cardiac catheterization showed a wedge pressure of 29 mm. Hg and a mean pulmonary artery pressure of 55 mm. Hg, rising to 85 mm. Hg on exercise. The cardiac index was 2.3 liters/min./sq.m. at rest and increased to 3.0 on exercise.

At operation, the valve orifice was estimated to be less than 1 sq. cm. in area. There was minimal regurgitation. It was estimated that the valve area was increased by operation to at least 2.5 cm., and after the procedure the left atrial pressure had decreased from 30 to 15 mm. Hg. The left atrial appendage showed no evidence of rheumatic activity.

The patient did quite well postoperatively. Seven months after operation, he was working actively on his farm. He noticed dyspnea only on unusual exertion such as running or walking uphill. He was not restricting his sodium intake.

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